REMARKS

Claims 1-43 are in the application. Claims 9, 18, and 29 have been withdrawn from consideration as being drawn to a non-elected species. Claims 42 and 43 are new independent claims. No new matter is added into the case in the new claims or in any amendments to any claims.

Claim 20 stands rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Claims 1-3, 6-8, 10-12, 15-17, 19-23, 26-28, and 30-41 were all said to be obvious under 35 U.S.C. §103(a) as from International Patent Publication Number WO 03/004599 A2 to Peleg et al. ("Peleg"), in view of Matsuda et al. (J. of Bacteriology, 1985, p. 1222-1228), or Ishii et al. (Journal of Fermentation and Bioengineering, 1994, p. 591-597), or Kim et al. (Biotechnology Letters 2001, p. 1067-1071). Claims 4, 5, 13, 14, 24, and 25 were also said to be obvious under 35 U.S.C §103(a) from Peleg in view of Matsuda or Ishii or Kim, and further in view of International Patent Publication Number WO 01/057217 to Kwon et al. ("Kwon").

Claim 20 is amended herein to, in essence, incorporate limitations of claim 21, which has been canceled without prejudice. Claims 6, 8, 9, 15, 17, 18, 26, 28, and 29 are amended to comply with USPTO rules regarding the identification of biological sequences and for purposes of clarification. Claims 1, 6, 10, 15, 16, 20, 26, and 27 are amended to italicize "*Pseudomonas diminuta.*" Claims 1, 10, and 20 are amended to grammatically clarify the claimed subject matter and to more particularly point out and distinctly define the claims. Claims 7, 8, 9, 16, 17, 18, 27, 28, and 29 are amended to clarify that two polynucleotides are recited in the claims. No new matter is added into the case by any of the present amendments.

All rejections are respectfully traversed. Reconsideration and favorable action are requested in light of the forgoing amendments and the remarks herein.

A. Claim 20 is Definite

Claim 20 is said to be indefinite for the alleged omission of an essential step. Without conceding this point, Applicants have rectified the alleged problem by amending the claim to include, in essence, the step of now canceled claim 21, said to be essential to claim 20. Accordingly, claim 20 as amended is more than sufficiently definite under 35 U.S.C. §112.

Reconsideration and allowance of claim 20 is hereby respectfully requested.

B. Claims 1-3, 6-8, 10-12, 15-17, 19-23, 26-28, and 30-41 are Patentable Over the Cited References

Applicants will now address the rejections of claims 1-3, 6-8, 10-12, 15-17, 19-23, 26-28, and 30-41 as allegedly obvious over Peleg in view of Matsuda or Ishii or Kim. Of these, claims 1, 10, and 20 are independent. Claim 1 is directed to an expression vector which comprises, among other things, a polynucleotide which encodes a fusion protein. The fusion protein includes a signal sequence of the gac gene of *Pseudomonas diminuta* (hereinafter "*P. diminuta*") and a polypeptide of interest other than the gac gene of *P. diminuta*. The signal sequence and the polypeptide of interest are linked in such a way that, upon expression of the polynucleotide as a fusion protein in a host cell, the signal sequence is cleaved off the fusion protein and the polypeptide of interest is released into the periplasm of the host cell. Claim 10 is directed to a prokaryotic host cell which, among other things, is transformed with the claimed expression vector. Claim 20 is directed to a process for making a polypeptide using such a prokaryotic host cell transformed using such an expression vector, in accordance with claim 10.

In an effort to show that Applicants' claims would have been considered obvious, the Examiner has assembled combinations of four different references. The primary reference, Peleg, does not teach, disclose, or suggest an expression vector that comprises a polynucleotide sequence that codes for a fusion protein which includes the claimed signal sequence of the gac gene of *P. diminuta*. Peleg deals with making a fusion polypeptide by introducing an expression construct containing a viral-derived peptide. Cited in combination with Peleg are Matsuda, Ishii, and Kim. However, Matsuda, Ishii, and Kim are not directed toward production of a polypeptide of interest, other than the gac gene of *P. diminuta*, as specifically called for in the claims. The references sought to be intermeshed with Peleg appear to be concerned with various disparate genetic and molecular biological characterizations of the gac gene in some species of *Pseudomonas*, and of the expression of gac protein in *E. coli*, but nothing in the combination or in any single reference reveals any motivation or suggestion that would have led a person of ordinary skill to modify Peleg to make an expression vector as called for in the claims.

The Examiner contends it would be obvious to substitute the gac signal sequence said to be described in Matsuda, Ishii, and/or Kim for the virally-derived signal sequence of Peleg in an expression vector for producing a polypeptide of interest according to Applicants' claims. However, the mere mention of the gac gene signal sequence in Matsuda, Ishii, or Kim cannot be

reasonably said to provide a motivation to modify Peleg and reconfigure it to make Applicants' invention as claimed. Applicants do not claim (nor could they) to have invented the gac gene. But there is plainly no suggestion in this group references to make Applicants' invention employing a fusion protein that includes a signal sequence of the gac gene of *P. diminuta* and a polypeptide of interest other than the gac gene of *P. diminuta* so as to cause the latter to be released into the paraplasm of the host cell as claimed.

It is well accepted in the art, that while many genetic recombinations "might" be useful, the science is generally not predictable. There would have been no reasonable expectation for success in substituting the gac signal sequence as claimed by Applicants into an expression vector according to the process of Peleg, absent some indication or direction from the references that such a substitution should be done or would work. But there is none. Ishii teaches that "the signal sequence is foreign to *E. coli* and not effectively recognized by *E. coli* signal peptidase" (page 596, last paragraph). Accordingly, the combined disclosure of Ishii and Peleg would actually have served to discourage a person of ordinary skill in the art who read these references from attempting to make the proposed combination, and would, if anything, have lead one away from Applicants' invention.

Even if a person having ordinary skill in the art was thinking about the gac signal sequence along the lines of Applicants' invention while reading Peleg, and there is no reason why they would, there is no lawful basis to say it would have been obvious for such a person to engage in speculative "cutting and pasting" the gac signal sequence in exchange for the virally-derived signal sequence of Peleg, since the latter is the main thrust of Peleg. There is no basis in any analogous teaching to motivate one to believe the system described by Peleg would be compatible with Applicants' claimed gac signal sequence, and there is nothing to suggest that a mere substitution of Peleg's virally-derived sequence with Applicants' claimed gac signal sequence would be desirable for producing a polypeptide of interest in the manner claimed.

Therefore, even if a person of ordinary skill in the art managed to somehow collect the cited references, there is no motivation or suggestion anywhere for combining the references in the manner imagined because the references are so divergent in their teachings that it would not be obvious to combine them in the proposed manner. The only way to arrive at the present claims from reading the cited references is through impermissible hindsight after having learned

of Applicants' disclosure. Accordingly, independent claims 1, 10, and 20 are patentably distinct over the assemblage of references.

Claims 2-3 and 6-8 depend from claim 1, claims 11-12, 15-17, and 19 depend from claim 10, and claims 21-23, 26-28, and 30-41 depend from claim 20. The dependent claims add further elements and limitations to the base claims, also not found in the references. According to the MPEP, if a base claim is patentable, then all claims dependent thereon are also patentable. Since independent claims 1, 10, and 20 have been shown to patentably distinguish from the prior art, all of their dependents should also be allowable. Hence, reconsideration and allowance of claims 1-3, 6-8, 10-12, 15-17, 19-23, 26-28, and 30-41 are respectfully requested.

C. Claims 4, 5, 13, 14, 24, and 25 are Patentably Distinct Over the Cited References

Claims 4, 5, 13, 14, 24, and 25 are dependent claims rejected as allegedly obvious from Peleg combined with Matsuda, Ishii, or Kim, and further in view of Kwon. However, there is, in the first place, no lawful reason to postulate that one of skill in the art would make the proposed combination of Peleg, Matsuda, Ishii, and Kim, as described in part B above. But, even if there was some motivation to combine these teachings to make an "obvious" combination, and there is not, there still is no teaching, suggestion, or disclosure within Kwon to lead one of skill in the art to make the presently imagined combination. Kwon is directed toward the expression, in *E. coli*, of a heterologous fusion protein comprising a polypeptide of interest and an *E. coli* heat stable enterotoxin II signal sequence. No indication is given in Kwon that any signal sequence not native to *E. coli* (such as the *P. diminuta*-derived signal sequence of the present claims) would be of any use in an expression system for producing a polypeptide of interest according to Applicants' claims. The mere fact that Kwon discloses hIFNα-2a and hIFNα-2b as a polypeptide of interest in one expression system says nothing about the performance of those proteins in other expression systems, or makes any suggestion as to what, if any, alternative expression system might be suitable.

Accordingly, a person of ordinary skill in the art reading Peleg, Matsuda, Ishii, Kim, together with Kwon (and there is no reason why they would choose these and then attempt to somehow combine them, out of the thousands and other references dealing with use of *E. coli* for genetic manipulations), would have no "obvious" reason to reconfigure isolated fragments of the references and then try to combine them in the manner imagined in the Examiner to arrive at the

present claims. Accordingly, reconsideration and allowance of claims 4, 5, 12, 14, 24, and 25 is respectfully urged.

CONCLUSION

Applicants assert that the specification and claims of the present application meet the requirements of 35 U.S.C. §§112, 102, and 103, and patentably distinguished from the prior art made of record. Applicants respectfully submit that a full and complete response to the office action is provided herein, and that the application is now fully in condition for allowance. Action in accordance therewith is respectfully requested.

In the event this response is not timely filed, Applicants hereby petition for the appropriate extension of time and request that the fee for the extension along with any other fees which may be due with respect to this paper be charged to our Deposit Account No. 122355.

Respectfully submitted,

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May 12, 2008
865-546-4305